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| EXAMINER | |
|---|---|
| VIVLEMORE, TRACY ANN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/828,395 | JACKSON ET AL. | |
| | Examiner | Art Unit | |
| | Tracy Vivlemore | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *4,5,9,10,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-8,11-13 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/16/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Specification*

The disclosure is objected to because of the following informalities: the specification recites at page 4 that exemplary non-cancerous angiogenesis-related diseases are listed in table 1. It appears that this reference should be to table 4 because table 1 actually shows the results of experiments described in example 1.

Appropriate correction is required.

### *Response to arguments: Claim Rejections - 35 USC § 112*

Claims 1, 6, 11 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection is maintained for the reasons set forth in the office action mailed December 27, 2005.

Applicants traverse the written description requirement by noting the specification expressly contemplates the use of other agents, specifically antibodies, which were known in the art at the time of filing of the instant application. The disclosure of antibodies to clusterin in the prior art is acknowledged but this disclosure, coupled with the disclosure of nucleic acid based inhibitors of clusterin in the specification does not provide a description of the large genus of compounds encompassed by the claims. As described in the original rejection and reiterated in the office action mailed February 28, 2007, the instant claims do not satisfy the written description requirement because the

description of antisense oligonucleotides and siRNAs targeted to human clusterin provided by the specification does not describe a representative number of the genus of inhibitors encompassed by the claims. The structure of an antisense oligonucleotide does not lead the skilled artisan to the structure of any other type of inhibitor that has the function of inhibiting clusterin in all species. Applicants' arguments do not address the relationship of the structure of the disclosed inhibitors and the claimed function of inhibiting clusterin for the purpose of treating disease and thus do not overcome the rejection of record.

Applicants request clarification of statement that "written description requires more than a mere statement that something is part of the invention." As described in MPEP 2163, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof.

***Claim Rejections - 35 USC § 112***

Claims 1-3, 6-8 and 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are directed to methods of reducing angiogenesis or treating a non-cancerous angiogenesis-related disease by reducing the amount of clusterin in an individual suffering from such a disease.

"Non-cancerous angiogenesis-related disease" is not a recognized term of art. The term "non-cancerous angiogenesis-associated diseases" is described at page 4 of the specification as referring to "non-cancerous diseases or conditions wherein inappropriate angiogenesis is observed as a symptom of the disease". It is assumed for the purposes of examination that this definition is also meant to serve for the term "non-cancerous angiogenesis-related disease".

The specification does not describe the nature of relationship to angiogenesis that is required in order for any particular disease to be an "angiogenesis-related disease". While the specification does state angiogenesis-related diseases exhibit "inappropriate angiogenesis", it is unknown whether "inappropriate" angiogenesis is limited to an undesired occurrence of angiogenesis or if a lack of angiogenesis can also be inappropriate, which would allow conditions resulting from lack of angiogenesis, such as ischemia, to be defined as "angiogenesis-related disease". Given the lack of definition of the term non-cancerous angiogenesis-related disease, the skilled artisan would be unable to recognize the metes and bounds of the claims because it is unknown what feature makes any particular disease angiogenesis-related. For example, table 4 lists dystrophic epidermolysis bullosa as one example of angiogenesis-related disease, but the teachings of the prior art regarding the role of angiogenesis in this disease is unclear. Arbiser et al. (Molecular medicine 1998, vol. 4, pages 191-195) suggest angiogenesis inhibitors as a treatment for dystrophic epidermolysis bullosa in

order to antagonize basic fibroblast growth factor, which may contribute to the increased fibroblast collagenase observed in patients who have this disorder. However, Sibbald et al. (Ostomy Wound Management 2005, vol. 51, pages 22-46) teach that wound healing is essential for treatment of dystrophic epidermolysis bullosa and that angiogenesis encourages wound healing. While dystrophic epidermolysis bullosa might be considered an angiogenesis-related disease, it is not clear whether angiogenesis in this condition is "inappropriate" and therefore it is not clear that inhibition of angiogenesis would be a beneficial treatment for this condition.

The term "non-cancerous angiogenesis-related disease" is so broad as to encompass a supergenus of widely disparate conditions lacking a common etiology. The wide variety of conditions encompassed by the term "non-cancerous angiogenesis-related disease" are so disparate in terms of cause, patient population, presence of other symptoms and disease progression that it is unlikely the single act of reducing the effective amount of clusterin will be sufficient to provide a therapeutic treatment for all such conditions. Due to the immense breadth of the genus of conditions contemplated as being treatable by the instantly claimed method and the lack of clarity of the term, the metes and bounds of the claims are unknown and would not allow the skilled artisan to immediately recognize whether they are infringing the claims.

***Response to Arguments***

In response to the 112, second paragraph rejection applicants have amended claims 1, 6 and 11 to more clearly define the angiogenesis-related diseases encompassed by the claims. While these amendments serve to narrow the scope of

the claims somewhat, it is not sufficient to overcome the indefiniteness rejection. The claims even as amended encompass a wide variety of conditions disparate in terms of cause, patient population, presence of other symptoms and disease progression that it is unlikely the single act of reducing the effective amount of clusterin will be sufficient to provide a therapeutic treatment for all such conditions. Additionally, as described in the body of the rejection, for some of the diseases contemplated as treatable by the instant method the desirability of reducing angiogenesis is unknown.

***Claim Rejections - 35 USC § 102***

Claims 1, 2, 6, 7, 11 and 12 are rejected under 35 U.S.C. 102(b) as anticipated by Monia et al. (of record).

Claims 1 and 11 are directed to methods of treating a non-cancerous angiogenesis-related disease by administering to an individual suffering from the non-cancerous angiogenesis-related disease a composition that reduces the amount of clusterin in the individual. In claim 11 the individual is a human. Claim 6 is directed to a method of reducing angiogenesis in a non-cancerous angiogenesis-related disease by treating cells associated with the non-cancerous angiogenesis-related disease with a composition that reduces the amount of clusterin. Claims 2, 7 and 12 depend from claims 1, 6 and 11, respectively and recite that the therapeutic composition is an antisense oligonucleotide complementary to SEQ ID NO: 1.

Monia et al. disclose antisense oligonucleotides targeted to human clusterin and methods of using these oligonucleotides. One of these antisense oligonucleotides is

designated as SEQ ID NO: 18, which is complementary to nucleotides 101-120 of instant SEQ ID NO: 1. At column 2, line 65 through column 3, line 6 Monia et al. disclose overexpression of clusterin is associated with atherosclerosis, a disease disclosed in the instant specification as being a non-cancerous angiogenesis-related disease. Monia et al. disclose at column 3, lines 40-46 a method of treating an animal, particularly a human, having a disease associated with expression of clusterin using the antisense oligonucleotides of their invention.

Claim 6 recites a method of reducing angiogenesis in cells associated with a non-cancerous angiogenesis-related disease by administering a composition effective to reduce the amount of clusterin in the cells. Monia et al. disclose antisense oligonucleotides that reduce the amount of clusterin and further disclose administering these oligonucleotides to an animal suffering from a disease associated with expression of clusterin. Monia et al. further disclose that atherosclerosis, a disease explicitly disclosed in the instant specification as an example of a non-cancerous angiogenesis-related disease, is one such disease associated with expression of clusterin. Therefore, although silent with regard to the ability of their method to reduce angiogenesis in a non-cancerous angiogenesis-related disease, because Monia et al. disclose administering a composition effective at reducing clusterin to the cells of an animal that is suffering from a non-cancerous angiogenesis-related disease and because performing this method would be treatment of cells associated with the disease, the method of Monia et al. would, absent evidence to the contrary, provide the recited effect of reducing the occurrence of angiogenesis.

Thus, Monia et al. disclose a method of inhibiting clusterin expression in disease-associated cells and individuals suffering from such diseases using an antisense oligonucleotide complementary to SEQ ID NO: 1 and anticipate claims 1, 2, 6, 7, 11 and 12.

***Response to arguments***

Applicants traverse the 102 rejection over Monia et al. by arguing it has not been shown that reduction of clusterin would necessarily treat atherosclerosis by a reduction of angiogenesis. Applicants further argue that clusterin was known to form a high density lipoprotein complex with apolipoproteins A-I in human plasma and was also known to play a role in lipid transport and lipid redistribution, activities having nothing to do with angiogenesis. Based on this reasoning, applicants assert the examiner has not met the burden of showing that reduction of angiogenesis would necessarily have occurred if the teaching of the prior art were followed.

This argument is not persuasive because Monia et al. disclose using antisense oligonucleotides targeted to clusterin for treatment of conditions associated with clusterin expression. One such disease is atherosclerosis, a disease disclosed in the instant application as a non-cancerous angiogenesis related disease. Since applicants themselves disclose atherosclerosis as a disease treatable by the instantly claimed methods and Monia disclose treatment of atherosclerosis with antisense oligonucleotides targeted to clusterin, an inherency rejection based on technical reasoning has been made and the burden has shifted to applicants to demonstrate that following the teaching of the prior art would not result in reduction of angiogenesis.

Applicants respond to the examiner's statements on page 12 of the previous office action by noting that "what Monia "may have thought" is not relevant, only what Monia actually says in the document relied upon is relevant to a rejection based on inherency. The examiner agrees that what Monia "may have thought" is irrelevant, however, it is noted that these statements were made in response to arguments provided at page 12 of the appeal brief.

***Claim Rejections - 35 USC § 103***

Claims 1-3, 6-8 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monia et al. as applied to claims 1, 2, 6, 7, 11 and 12 above, and further in view of Gleave et al. (WO 00/49937, of record).

The claims are directed to methods of treating or reducing angiogenesis in a non-cancerous angiogenesis-related disease by administering a composition that reduces the amount of clusterin. In specific embodiments the therapeutic composition is an antisense oligonucleotide complementary to SEQ ID NO: 1 and the individual treated is a human. Claims 3, 8 and 13 recite that the antisense oligonucleotide is SEQ ID NO: 5.

The teachings of Monia et al. are described in the 102 rejection over this reference. Monia et al. do not teach the use of SEQ ID NO: 5 to inhibit clusterin.

Gleave et al. teach clusterin is a ubiquitous protein with a diverse range of proposed activities. Gleave et al. further teach inhibition of clusterin using antisense oligonucleotides for the purpose of treating prostate cancer. One of the antisense oligonucleotides targeted to clusterin, SEQ ID NO: 4, is identical to SEQ ID NO: 5 of the

instant application. Gleave et al. teach in figure 3 and on page 7 that in prostate tumor cells SEQ ID NO: 4 provides the most effective downregulation of clusterin expression.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the antisense oligonucleotide designated as SEQ ID NO: 4 by Gleave et al. in the method of reducing clusterin expression in an animal suffering from a disease associated with clusterin expression such as atherosclerosis as taught by Monia et al. Monia et al. provide a motivation to use antisense oligonucleotides to treat diseases such as atherosclerosis that are associated with clusterin expression by explicitly suggesting such treatment while Gleave et al. provide a motivation and reasonable expectation of success in using the sequence designated as SEQ ID NO: 4 by teaching this antisense sequence is particularly effective in downregulating expression of clusterin.

Thus, the invention of claims 1-3, 6-8 and 11-13 would have been obvious, as a whole, at the time the invention was made.

***Response to Arguments***

Applicants traverse the 103 rejection by noting this rejection depends on Monia for the teaching of atherosclerosis and the extension that this inherently is a teaching relevant to angiogenesis. Applicants assert this rejection should be withdrawn for the same reasons as the anticipation rejection. This argument is not persuasive for the reasons described above in the response to arguments for the 102 rejection.

***New Claim Rejections - 35 USC § 103***

Claims 1-3, 6-8, 11-13 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brooks et al. (US 5,766,591) in view of Millis (US 6,464,975) and Gleave et al. (of record).

The claims are directed to methods of treating or reducing angiogenesis in a non-cancerous angiogenesis-related disease by administering a composition that reduces the amount of clusterin. In specific embodiments the therapeutic composition is an antisense oligonucleotide complementary to the sequence of human clusterin and the individual treated is a human. Claims 3, 8 and 13 recite that the antisense oligonucleotide is SEQ ID NO: 5. Claims 16-18 recite specific diseases treatable by the instantly claimed methods, including rheumatoid arthritis, psoriasis, diabetic retinopathy, and macular degeneration.

Brooks et al. teach at columns 7-9 that angiogenesis, a process of tissue vascularization that involves the growth of new developing blood vessels into a tissue, is an important process in wound healing and in the pathogenesis of a large variety of clinical diseases. Brooks et al. further teach that where growth of new blood vessels is the cause of, or contributes to, the pathology associated with a disease, inhibition of angiogenesis will reduce the deleterious effects of the disease in a patient. Examples of diseases in which angiogenesis is believed to be important, referred to as angiogenic diseases, include rheumatoid arthritis, psoriasis diabetic retinopathy, hemangiomas and macular degeneration. Brooks et al. do not teach that angiogenesis can be inhibited by inhibition of clusterin.

Millis teaches that clusterin is a protein essential for VSMC migration and reorganization. In cultured vascular smooth muscle cells (VSMC) a substantial increase in synthesis and secretion of clusterin occurs during the time when the culture modulates from a proliferating monolayer morphology to nodular cell culture morphology, a process that model some aspects of in vivo vascular remodeling that occurs in response to injury. Millis teaches that clusterin itself can be used to initiate tissue remodeling by VSMC, wound healing and angiogenesis while antisense sequences of the gene that encodes clusterin function to inhibit cell migration and differentiation. Millis teaches that compositions can be used for inhibition or enhancement of angiogenesis. Use of compositions to enhance migration can be used to initiate the process by which new blood vessels are formed. For example a therapeutically effective amount of a migration-altering composition such as clusterin administered directly to the site of a vascular blockage facilitates development of new blood vessels. Millis further teaches that inhibition of clusterin inhibits angiogenesis. Angiogenesis is important in tumor growth and compositions that inhibit clusterin for example, antisense polynucleotides derived from the sequence of clusterin, have use as anti-tumor agents.

Gleave et al. teach clusterin is a ubiquitous protein with a diverse range of proposed activities. Gleave et al. further teach inhibition of clusterin using antisense oligonucleotides for the purpose of treating prostate cancer. One of the antisense oligonucleotides targeted to clusterin, SEQ ID NO: 4, is identical to SEQ ID NO: 5 of the instant application. Gleave et al. teach in figure 3 and on page 7 that in prostate tumor cells SEQ ID NO: 4 provides the most effective downregulation of clusterin expression.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to a treat disease associated with undesired angiogenesis as taught by Brooks et al. using an antisense oligonucleotide as taught by Millis to inhibit clusterin expression for the purpose of inhibiting angiogenesis. It would have further been obvious to use SEQ ID NO: 5 as the antisense oligonucleotide in the method. Brooks et al. provide a motivation to reduce angiogenesis in disease states associated with undesired angiogenesis by explicitly teaching that inhibition of angiogenesis will reduce the deleterious effects of such diseases in a patient. Based on the teachings of Millis that inhibiting clusterin using antisense oligonucleotides reduces cell migration and therefore reduces angiogenesis and the teachings of Gleave et al. of an antisense oligonucleotide that successfully inhibits clusterin expression, one of ordinary skill in the art would have been motivated and had a reasonable expectation of success in using antisense oligonucleotides such as SEQ ID NO: 5 to treat an angiogenesis related disease through inhibition of clusterin expression.

Thus, the invention of claims 1-3, 6-8, 11-13 and 16-18 would have been obvious, as a whole, at the time the invention was made.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
July 16, 2007

RICHARD SCHNIZER, PH.D.
PRIMARY EXAMINER